38. (Amended) The fusion protein of claim 18, wherein said first polypeptide comprises at least amino acids [14] 38 to [150] 174 of streptavidin, as set forth in SEQ ID NO: 2 [Figure 4].

39. (Amended) The fusion protein of claim 18, wherein the first polypeptide comprises at least amino acids selected from the group consisting of [1] 25 to [158] 182, [5] 29 to [158] 182, [14] 38 to [150] 174, [14] 38 to [151] 175, [14] 38 to [152] 176, [14] 38 to [153] 177, [14] 38 to [154] 178, [14] 38 to [155] 179, [14] 38 to [156] 180, [14] 38 to [157] 181, or [14] 38 to [158] 182 of streptavidin, as set forth in SEQ ID NO: 2 [Figure 4].

REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested. Claims 18-39 and 65 are presently under prosecution in the present application. Claims 1-17, 40-64, and 66 stand withdrawn from further consideration pursuant to 37 C.F.R. §1.142(b), as being drawn to a nonelected invention. Claims 18, 21-24, 26, 32-34, 38, and 39 have been amended to more particularly point out certain aspects of the present invention. Support for the amendments can be found throughout the specification and at specific sections as noted in the following remarks. Support for the use of "humanized" is provided by "humanized" and "mouse-human" on page 8, line 2 and by the more specific example, "Primatized™", on page 8, line 2 (as amended). Support for variants comprising at least 90% amino acid identity with the native sequence of streptavidin is provided, for example, on page 6, line 26 through page 7, line 3. Support for variants that retain the ability to bind biotin is provided on page 9, lines 16-18 and page 11, lines 1-12. Support for antigen-binding fragments of an antibody is provided on page 8, lines 6-11. Support for a fusion protein capable of forming a tetrameric complex similar to that of native streptavidin is provided on page 9, lines 20-24. Support for an antibody or fragment thereof that specifically binds a cell surface protein or a cell-associated stromal or matrix protein is provided on p. 21, lines 5-13. Support for the sequence listing Gly-Gly-Gly-Gly-Ser, SEQ ID NO:47, is provided by $(Gly_4Ser)_x$ on page 18, line 28. Non-elected claims 1-17, 40-64, and 66 have been canceled. No new matter has been added.

Restriction Requirement/Election

A telephonic restriction requirement was imposed on March 30, 2001 at which the Examiner requested that Applicants choose between Group I: Claims 1-17 and 66 drawn to a vector construct and host cell comprising said vector construct; Group II: Claims 18-39 and 65, drawn to fusion proteins; Group III: Claims 40-63, drawn to a method for targeting a tumor cell; and Group IV: Claim 64, drawn to a method for constructing a tetravalent antibody. In a teleconference of that same date, Applicants provisionally elected Group II, with traverse. Accordingly, Applicants hereby affirm the election of Group II and, thus, have canceled claims unrelated to this election.

Objection to the Specification

The Examiner objects to the use of the word primatized in the application and points out that Primatized™ is a trademark, which should be capitalized wherever it appears and be accompanied by the generic terminology.

Applicants submit that the term "primatized' was used generically to describe any antibody comprising a region derived from a primate, including, for example, humanized and Primatized™ antibodies. In light of the trademark Primatized™, Applicants have amended the application to replace the word "primatized" with "Primatized™" on page 8, line 2. In addition, Applicants have requested the application be amended to include generic terminology corresponding to Primatized™, immediately following use of the trademarked term on page 8, line 2. To reconcile the intended use of the word primatized as encompassing humanized, Applicants have also requested the application be amended to separately list "humanized" within the definition of antibody on page 8. Applicants have also amended claim 34 such that the word "primatized" is replaced with the word "humanized." Applicants note that these amendments do not introduce new matter. Rather, they provide a generic description of the trademarked term "Primatized™" and alter the language of the claim to reconcile the intended use of "primatized" as a generic term with the trademarked use of "Primatized™." Support for the use of "humanized" is provided by "humanized" and "mouse-human" on page 8, line 2 and by the more specific example, "Primatized™", on page 8, line 2 (as amended).

Applicants respectfully request that the Examiner withdraw this objection to the specification, as the basis of the objection is obviated upon entry of the requested amendments.

Objection to the Claims

The Action objects to an alleged informality of claim 32, which recites a limitation containing an amino acid sequence of more than four amino acid residues. The Action states that the claim contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §1.821(a)(1) and (a)(2) and that the claim is not written in a manner that complies with the requirements of 37 C.F.R. §1.821-1.825.

In response, Applicants hereby submit the accompanying sequence listing, SEQ ID NO:47, and request that it be added to the previously submitted Sequence Listing. SEQ ID NO: 47 recites the amino acid sequence Gly Gly Gly Gly Ser, which is identical to the sequence provided in claim 32, prior to amendment. This submission includes no new matter. In compliance with 37 C.F.R. §1.821-1.825, the Sequence Listing, as amended, is also provided in computer readable form.

Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 18-39 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. In particular, the Action states the art of protein engineering is unpredictable and the specification lacks sufficient guidance for one skilled in the art to make all of the claimed fusion proteins with a reasonable expectation of success and without undue experimentation. Furthermore, the Action asserts that the teachings of the specification are insufficient to demonstrate the utility of all fusion proteins of the invention.

Applicants respectfully traverse this ground for rejection and submit that the instant specification does, in fact, provide the requisite degree of enablement and utility for claims directed to a fusion protein comprising at least 129 amino acids of streptavidin and any other peptide. Applicants submit that the specification adequately provides one skilled in the art the necessary teachings to practice the claimed invention, including the generation of genomic streptavidin fusion proteins with a reasonable expectation of success. Furthermore, Examples I-X of the instant specification provide specific support for practicing the claimed invention. In addition, Applicants submit that the fusion proteins and compositions of the invention possess the requisite utility under 35 U.S.C. §112. Remarks specifically addressing each of the alleged deficiencies cited in the Action are provided below.

First, the Action objects to claims encompassing a fusion protein comprising at least 129 amino acids of streptavidin and *any other polypeptide*, since the specification allegedly describes only fusion proteins comprising this region of streptavidin and a single-chain antibody.

Applicants respectfully traverse this ground for objection and point out that numerous examples of the construction and expression of streptavidin fused to proteins other than antibodies are provided, both in the Background of the Invention, p. 1, line 25 – p. 2, line 7, and in the scientific literature. For example, Ohno and Meruelo, cited in the Background of the Invention, p. 2, lines 4 and 5, describe expression of streptavidin core fused to tumor growth factor alpha. In addition, a cursory scan of the scientific literature revealed numerous streptavidin fusion proteins, including: trypsin-streptavidin fusion protein (Clare, D.A. *et al.*. Enzyme Microb Technol 2001 Apr 5;28(6):483-491); streptavidin-luciferase fusion protein produced by insect cells using the baculovirus expression system (Karp M. and Oker-Blom, C. Biomol Eng 1999 Dec 31;16(1-4):101-4); and streptavidin-Protein A fusion protein (Yu A, *et al.*. DNA Cell Biol 2000 Jul;19(7):383-8). Furthermore, fusion proteins and methods of expressing fusion proteins are widely known by those of ordinary skill in the art, as demonstrated by the numerous fusion protein expression constructs commercially available. In addition, the specification specifically teaches streptavidin expression cassettes and vector constructs, as well as methods of expressing and producing fusion proteins (p. 8, line 16 – p. 17, line 10). The specification also provides numerous working examples, demonstrating successful expression of streptavidin fusion proteins (Examples I-X). Applicants respectfully submit that any experimentation performed to analyze or optimize the expression system for a particular genomic streptavidin fusion would be expected by one of skill in the art and that appropriate methods are well known in the art. Further, Applicants submit that methods of testing the ability of a fusion protein to bind biotin and maintain solubility in the periplasmic space are well known in the art, and support for this can be found at lines 16-19, page 9, and lines 1-12, page 11 of the instant specification. Such testing or screening would be considered merely routine, rather than undue, experimentation. Thus, Applicants assert that one of skill in the art would be able to express the streptavidin fusion proteins of the present invention with a reasonable expectation of success, based upon the teaching of the specification and the scientific literature.

The Action also alleges that the teachings of the specification are insufficient because one of skill in the art cannot immediately appreciate the utility of a fusion protein comprising streptavidin and *any* polypeptide or the utility of a fusion protein comprising streptavidin and *any* fragment of an antibody, particularly if said fragment does not have antigen-binding activity. The Action also appears to assume that a useful genomic streptavidin fusion protein would require the fused polypeptide to retain its functionality when fused to streptavidin. In addition, the Action alleges that a V_L-V_H B9E9 scFvSA fusion protein cannot be produced in a sufficient quantity to be useful.

Applicants respectfully traverse this ground for rejection and submit the claimed invention possesses the requisite utility, as disclosed in pages 1-3 and Examples I-X of the specification. Briefly, the fusion protein constructs described in the specification provide an easy, cost effective, and scaleable method for the production of streptavidin fusion proteins. The methods employed in the instant specification allow for production of genomic streptavidin fusion proteins that are secreted to the periplasmic space of bacteria or the culture medium without the rigor and expense of purifying the protein from inclusion bodies, as is necessary with fusion proteins generated by expressing a core streptavidin-containing construct. Thus, the genomic streptavidin fusion proteins of the invention possess the advantage of being more readily and less expensively purified than previous streptavidin fusion proteins.

Furthermore, Applicants contend that the usefulness of polypeptides lacking one or more wild type functions is widely known and acknowledged by those of skill in the art. For example, dominant-negative and inhibitory mutants of transcription factors, kinases, and cell-surface receptors are widely used by those of skill in the art. However, with regard to the antibody fragment, Applicants, while not acquiescing to the rejection, have amended claim 23 to recite "antigen-binding fragment", solely to expedite prosecution of the application. Support for such functional derivatives can be found on page 17 of the instant specification.

Regarding the Actions's concern with respect to the level of fusion protein expression achieved by the current invention, Applicants contend that methods of using the disclosed invention do not necessitate any particular level of expression. Certainly, there is no need to produce fusion protein in an amount appropriate for large-scale therapeutic uses of the invention, as the specification and claims are not limited to such uses. In addition, there is no

indication that a specific therapeutic use would require levels of expression higher than that disclosed in the specification. Thus, Applicants submit that a particular level of expression is not required for enablement of the claims.

In summary, Applicants submit that adequate support is evident in the specification for the utility of genomic streptavidin fused to a second polypeptide in the generation of the fusion proteins of claims 18-39 and that one of ordinary skill in the art would readily appreciate the utility of the invention upon review of the specification.

The Action also alleges that claims reciting a single-chain antibody in which the variable light chain and the variable heavy chain are not separated by a linker lack enablement. Similarly, the Action alleges that claims reciting a single-chain antibody in which the variable light chain and the variable heavy chain are separated by *any* linker lack enablement. In addition, the Action alleges that one skilled in the art cannot predict which fusion proteins comprising a variable light chain and a variable heavy chain in any orientation will be capable of being produced in sufficient quantity to be useful or whether such fusion proteins will be stable and retain the recognition properties of the parental antibody.

Applicants respectfully traverse this ground for rejection. Applicants submit that support for streptavidin fusion proteins of varying linker length can be found on pages 11-12 and Examples I, II, and IV of the instant specification. Applicants further submit that the optimal length of a linker and the order of the variable subunits of the antibody are easily determined experimentally. Support for such routine screening of fusion proteins can be found on pages 19-21, and Examples I, II, and IV of the instant specification. Furthermore, Applicants, while not acquiescing to this basis of rejection, have amended claim 23 to recite "antigen-binding", solely to expedite prosecution of the application.

In addition, as described by the Action, Example IV provides examples of a number of genetic variants constructed using linkers of different lengths and composition and the variable regions in different orientations. Applicants submit *all* constructs produced protein when expressed in bacteria, as indicated in Table 1, page 37 of the specification. Likewise, Example V describes fusion proteins produced as described in the instant specification, with and without co-expression of the protein-folding gene *fkpA*. As indicated in Table 2, page 39 of the specification, expression of the fusion protein constructs increased or remained the same in nine

out of eleven samples tested. Applicants submit these examples, like all examples in the specification, illustrate the specification adequately enables one skilled in the art to generate fusion protein constructs, as described in the instant specification, with a reasonable expectation of success.

The Action also alleges the claimed invention cannot be practiced without undue experimentation. In particular, the Action cites Chilkoti *et al.*. (*Bio/Tech. 13*: 1198-1204, 1995) and alleges one skilled in the art cannot determine whether a particular fusion protein comprising streptavidin retains its ability to form tetramers and to bind biotin, without undue experimentation. Applicants respectfully submit that methods for testing the ability of a fusion protein construct to bind biotin and maintain solubility in the periplasmic space of bacteria are well known in the art and only amount to routine screening. Applicants submit support for this can be found at lines 16-19, page 9, and lines 1-12, page 11 of the instant specification. Furthermore, while it is not necessary for the fusion protein constructs to bind biotin in order to practice the claimed invention, nevertheless the claims have been amended to include this embodiment while not acquiescing to any rejections thereon. Applicants submit one skilled in the art could practice the claimed invention without undue experimentation.

Claim 65 stands rejected under 35 U.S.C. §112, first paragraph for allegedly lacking enablement. In particular, the Action states that the specification does not provide adequate guidance to enable one skilled in the art to use a pharmaceutical composition formulated from claims 18-39 to treat or diagnose a medical condition in a subject, particularly a human subject, without undue experimentation. The Action also states the working examples provided are insufficient to enable human treatment.

Applicants respectfully submit that while therapeutic and diagnostic uses are contemplated by the invention, the invention also encompasses other uses, including, for example, the targeting and delivery of streptavidin fusion proteins. To more clearly convey the full scope of the invention, Applicants, while not acquiescing to this basis of rejection, have amended claim 65 to recite "a composition," rather than "a pharmaceutical composition." Nonetheless, Applicants submit that support for multiple therapeutic uses of pharmaceutical compositions of the claimed invention can be found on pages 21-28, and Examples VIII-X of the instant specification. Examples VIII-X indicate streptavidin fusion proteins generated as

described in the specification are able to selectively bind tumor grafts *in vivo*. Applicants submit that extrapolating such treatments to humans would involve only routine screening, and that human clinical trials are not required for patent issuance. In accord with the teachings of the specification at page 27, lines 19 – 30, the determination of the optimal dosage and treatment schedule is well known in the art. Thus, Applicants submit that one of ordinary skill in the art would be able to practice the invention without undue experimentation.

Applicants submit that the claimed invention fully satisfies the enablement requirement of 35 U.S.C. §112, first paragraph, and respectfully request these rejections be withdrawn.

Rejection under 35 U.S.C. §112, First Paragraph, Written Description

Claims 18-22, 38, 39, and 65 stand rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants respectfully traverse this ground for rejection and submit that the written description requirement has been satisfied. Applicants submit that one of ordinary skill would be apprised that the inventors were in possession of all aspects of the invention, including the claimed genomic streptavidin fusion proteins and compositions thereof. The nucleotide and amino acid sequences of genomic streptavidin are fully disclosed in the application (pages 8 and 9; Figure 4). In addition, the detailed description of the invention provides expression vector constructs suitable for expression of the streptavidin fusion proteins of the invention, as well as methods of preparing genomic streptavidin fusion protein constructs, expressing the encoded fusion proteins, and purifying the expressed proteins (pages 9-17). The disclosure also demonstrates reduction to practice of numerous genomic streptavidin fusion proteins, comprising various linker sequences and orientations (Examples 4 and 5). Given the high level of skill and knowledge in the art related to fusion protein expression, the disclosure provides a representative number of species sufficient to support the claimed genus. Applicants submit that the instant specification provides sufficient identifying and functional characteristics, such as sequence and

binding characteristics, to inform one of ordinary skill in the art that the applicant was in possession of the claimed invention.

In addition, support for uses of genomic streptavidin expressed fusion constructs can be found on pages 21-28 of the instant specification. In particular, the specification describes methods for targeting particular sites or tumors in a mammalian host (pg. 21), as well as "pre-targeting" a site followed by a clearing diagnostic or therapeutic agent capable of binding to the "pre-targeted" moiety at the target site (pg.22-23). Additionally, the specification describes the use of genomic streptavidin fusion proteins with diagnostic or therapeutic agents including radionuclides, toxins, anti-tumor agents, drugs (including conventional chemotherapeutics), genes, and cytokines (pg. 25-27). Applicants submit both the level of ordinary skill in the art and the basic techniques necessary to practice the invention are known in the art. Therefore, Applicants respectfully submit that the invention is adequately disclosed and one of ordinary skill in the art would understand that Applicants were in possession of the claimed invention and be adequately informed as to how to practice the claimed invention. Thus, Applicants submit the written description requirement of 35 U.S.C. §112, first paragraph, has been met and respectfully request this rejection be withdrawn.

Rejection under 35 U.S.C. §112, Second Paragraph, Indefiniteness

Claims 18-39 and 65 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. Applicants submit that one of ordinary skill in the art would be reasonably apprised by the claims of the metes and bounds of the invention. Nonetheless, solely to expedite prosecution of the application, Applicants have amended certain claims. Applicants' responses to specific indefiniteness objections raised by the Action are detailed below.

The Action states claims 18, 24, 38, and 39 are indefinite for reciting "streptavidin, Figure 4."

Applicants respectfully traverse this ground for rejection and submit that one of skill in the art would clearly understand that claims indicating polypeptide sequences referred to the amino acid sequence presented in Figure 4. Nonetheless, solely to expedite prosecution of the application, Applicants have followed the Examiner's suggestion and claims 18, 24, 38, and 39 have been amended to recite "SEQ ID NO:2." SEQ ID NO:2 contains only amino acid

sequence. In addition, the amino acid numbers referenced in claims 38 and 39 have been amended as necessary to preserve the meaning of the claims, since the numbering in Figure 4 and the numbering in SEQ ID NO:2 begin at different amino acid residues.

The Action further alleges claims 18 and 24 are indefinite because the claims recite "a first and a second polypeptide joined end to end".

Applicants traverse this basis of objection and submit that one skilled in the art would be reasonably apprised of the metes and bounds of the invention. One of skill in the art would understand the phrase "a first and a second polypeptide joined end to end" is merely meant to distinguish one polypeptide from the other and is not limiting with regard to the orientation of the polypeptides relative to one another within the fusion protein. Support for this interpretation can be found on page 3, lines 10-17 and page 11, lines 21-24 of the instant specification.

The Action also alleges that claim 18 is vague and indefinite, since the claim recites the phrase "functional variant."

Although Applicants submit that one of skill in the art would understand the metes and bounds of the claim, Applicants have amended claim 18 to recite the specific function of binding biotin, both for clarification and to expedite prosecution. Support for this amendment may be found throughout the specification, including on page 9, lines 16-19. Thus, no new matter is introduced by the amendment.

The Action alleges claims 21, 22, and 65 are indefinite because claim 21 recites "between four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, and twenty amino acids," and claim 22 recites "between five to ten." The Action states such phrases are unclear as to what the values of the range are and whether the range includes values less than whole integers.

While Applicants submit one skilled in the art would understand the phrase of claims 21 and 22, Applicants have amended claims 21 and 22 as suggested by the Examiner, solely to expedite prosecution of the application. Claim 21, as amended, recites "wherein the linker consists of four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, or twenty amino acids." Claim 22, as amended, recites "wherein the linker is between five and ten amino acids."

The Action alleges claim 23 is vague and indefinite for reciting "a fragment thereof," claim 24 is vague and indefinite for reciting "capable of forming a tetrameric complex," and claim 26 is indefinite for reciting the phrase "(scFv)."

Applicants submit these particular phrases are readily understood by one skilled in the art. In particular, Applicants submit that scFv is a short form or abbreviation of single chain Fv that is widely known and accepted in the art. However, the claims have been amended for clarification and solely to expedite prosecution of the application. In accordance with the Examiner's suggestions, claim 23, as amended, recites "an antigen-binding fragment thereof." Claim 24, as amended, recites "capable of forming a tetrameric complex similar to that of native streptavidin," and claim 26, as amended, recites "a single-chain Fv fragment."

Furthermore, the Action alleges claims 33-37 are vague and indefinite because the claims recite "is specific for a cell surface protein or a cell-associated stromal or matrix protein."

Applicants submit one skilled in the art would understand the metes and bounds of the claims as written. However, the claims have been amended in order to facilitate prosecution of the application. Claim 33, as amended, recites "wherein the antibody or fragment thereof specifically binds a cell surface protein or a cell-associated stromal or matrix protein." The phrase "or fragment thereof" is introduced for clarification and does not introduce new matter.

Finally, the Action alleges that claim 34 is indefinite because of the use of the trademark "Primatized™." Applicants submit claim 34 has been amended to remove the trademark and to recite "humanized," in order to reconcile the trademarked meaning of Primatized™ with the intended scope of the claim. Support for this amendment can be found on page 8 of the specification.

Therefore, Applicants respectfully submit the indefiniteness rejections under 35 U.S.C. §112, second paragraph, have been overcome and request these rejections be withdrawn.

Rejection under 35 U.S.C. §103(a), Obviousness

Claims 18-39 and 65 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Dubel, *et al.* (J. Imm. Meth. 178: 201-209, 1995), as evidenced by Kipriyanov, *et al.* (Hum. Antibod. Hybrid. 6: 93-101, 1995), in view of Desplancq, *et al.* (Prot. Eng. 7: 1027-

1033, 1994), Anderson, *et al.* (Clin. Immnol. Immunopath. 84: 73-84, 1997), McLaughlin, *et al.* (Onc. 12: 1763-1769, 1998), the internet edition of the Bioprobe BV Catalog of Mouse Hybridomas (Bandung, Indonesia), Gallizia *et al.* (Prot. Exp. Pur. 14: 192-196, 1998), and Pahler, *et al.* (J. Biol. Chem. 262: 13933-13937, 1987), Aragarana, *et al.* (Nuc. Acids Res. 14: 1871-1882, 1986), Ohno *et al.* (DNA and Cell Biol. 15: 401-406, 1996), and Goshorn, *et al.* (Canc. Res. 53: 2123-2127, 1993).

Applicants respectfully submit that the Action has not established a *prima facie* case of obviousness, as the cited references, either alone or in combination, do not teach or suggest all elements of the claimed invention. Applicants submit the presently claimed invention uses a genomic streptavidin expressed gene fusion protein, comprising at least 129 amino acids of streptavidin. Applicants point out that none of the references cited by the Action disclose or teach this genomic streptavidin fusion protein. Indeed, the Action concedes that Dubel *et al.*, the primary reference cited, do not teach the first polypeptide of the fusion protein comprising at least 129 amino acid residues of streptavidin or at least amino acids 14-150 of streptavidin. Applicants submit the deficiencies of Dubel *et al.* are not remedied by any of the cited prior art references, as none of these references teach the use or advantages of genomic streptavidin fusion proteins.

Applicants submit streptavidin fusion proteins of the invention, comprising at least 129 amino acids of streptavidin, are non-obvious in light of the prior art's use of fusion proteins comprising core streptavidin, amino acids 14-136. Applicants submit genomic streptavidin fusion proteins provide substantial and heretofore unrecognized advantages over core streptavidin fusion proteins, including protein folding and secretion into the periplasmic space. Such advantages circumvent the need to extract the protein from the cytoplasm, as necessary for core-streptavidin fusion proteins. Applicants submit the use of genomic streptavidin in fusion proteins remedies a short-coming of using core-streptavidin in fusion proteins and was surprising in light of the prior art, which consistently used core-streptavidin. Applicants further submit that none of the cited references teach or suggest that the introduction of additional amino acid residues to the amino- or carboxy-terminal end of core streptavidin would provide the advantages demonstrated in the instant application. Such unexpected findings

clearly render the presently claimed invention non-obvious in light of Dubel, *et al.*, or any of the cited prior art references.

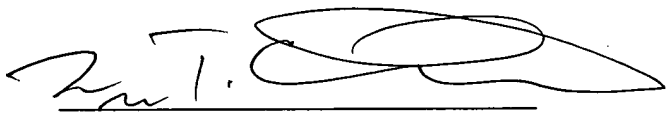
Applicants submit that the claims are nonobvious under 35 U.S.C. §103(a). Applicants respectfully request this basis of rejection be withdrawn.

Applicants respectfully submit that all claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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Enclosures:

- Postcard
- Check
- Sequence Listing
- Declaration re Sequence Listing
- Computer Diskette
- Form PTO/SB/21
- Form PTO/SB/17 (+ copy)
- Petition for an Extension of Time

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The following section has been added immediately after the title (page 1, lines 1 and 2):

CROSS-REFERENCE TO RELATED APPLICATION

The present application claims the benefit of priority from U.S. Application No. 60/168,976, filed December 3, 1999, now abandoned, and U.S. Application No. 60/137,900, filed June 7, 1999, now abandoned. All prior applications are hereby incorporated herein by reference.

Paragraph beginning at line 1 of page 8 has been amended as follows:

An "antibody," as used herein, includes both polyclonal and monoclonal antibodies; [primatized (*e.g.*, humanized)] Primatized™ (*i.e.* macaque V region fused to human constant domain; Newman *et al.*. 1992. *Bio/Technology 10:1455*); humanized; murine; mouse-human; mouse-primate; and chimeric; and may be an intact molecule, a fragment thereof (such as scFv, Fv, Fd, Fab, Fab' and $F(ab)'_2$ fragments), or multimers or aggregates of intact molecules and/or fragments; and may occur in nature or be produced, *e.g.*, by immunization, synthesis or genetic engineering; an "antibody fragment," as used herein, refers to fragments, derived from or related to an antibody, which bind antigen and which in some embodiments may be derivatized to exhibit structural features that facilitate clearance and uptake, *e.g.*, by the incorporation of galactose residues. This includes, *e.g.*, F(ab), $F(ab)'_2$, scFv, light chain variable region (V_L), heavy chain variable region (V_H), and combinations thereof.

In the Claims:

Claims 1-17, 40-64, and 66 have been canceled without prejudice.

Claims 18, 21-24, 26, 32, 33, 34, 38, and 39 have been amended as follows:

18. (Amended) A fusion protein, comprising at least a first and a second polypeptide joined end to end, wherein said first polypeptide comprises at least 129 amino acids of streptavidin, as set forth in SEQ ID NO:2 [Figure 4], or functional variants, said variants

comprising at least 90% amino acid identity with the native sequence thereof, wherein said variants retain the ability to bind biotin, and wherein said second polypeptide comprises an amino acid sequence differing by at least one residue from said first polypeptide.

21. (Amended) The fusion protein of claim 20, wherein the linker [is between] consists of four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, [and] or twenty amino acids.

22. (Amended) The fusion protein of claim 21, wherein the linker is between five [to] and ten amino acids.

23 (Amended) The fusion protein of claim 18, wherein said second polypeptide is an antibody or [a] an antigen-binding fragment thereof.

24. (Amended) The fusion protein of claim 23, wherein said fusion protein is capable of forming a tetrameric complex similar to that of native streptavidin with a second, third, and fourth fusion protein, said second, third, and fourth fusion protein comprising at least a first and a second polypeptide joined end to end, wherein said first polypeptide comprises at least 129 amino acids of streptavidin, as set forth in SEQ ID NO:2 [Figure 4], or functional variants, said variants comprising at least 90% amino acid identity with the native sequence thereof, wherein said variant retains the ability to bind biotin, and wherein said second polypeptide comprises an amino acid sequence differing by at least one residue from said first polypeptide.

26. (Amended) The fusion protein of claim 23, wherein the antibody is a single-chain Fv fragment [scFv].

32. (Amended) The fusion protein of claim 31, wherein the linker comprises at least four [Gly_4Ser linkers] repeats of SEQ ID NO: 47.

33. (Amended) The fusion protein of claim 23, wherein the antibody or fragment thereof [is specific for] specifically binds a cell surface protein or a cell-associated stromal or matrix protein.

34. (Amended) The fusion protein of claim 33, wherein the antibody or fragment thereof is a [primatized] humanized antibody.

38. (Amended) The fusion protein of claim 18, wherein said first polypeptide comprises at least amino acids [14] 38 to [150] 174 of streptavidin, as set forth in SEQ ID NO: 2 [Figure 4].

39. (Amended) The fusion protein of claim 18, wherein the first polypeptide comprises at least amino acids selected from the group consisting of [1] 25 to [158] 182, [5] 29 to [158] 182, [14] 38 to [150] 174, [14] 38 to [151] 175, [14] 38 to [152] 176, [14] 38 to [153] 177, [14] 38 to [154] 178, [14] 38 to [155] 179, [14] 38 to [156] 180, [14] 38 to [157] 181, or [14] 38 to [158] 182 of streptavidin, as set forth in SEQ ID NO: 2 [Figure 4].